S/N 09/647,054 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Peter Joseph Cassidy, et al.	Examiner: Christopher M. Gross
Serial No.:	09/647,054	Group Art Unit: 1639
Filed:	March 24, 1998	Docket No.: 707.025US1
Title:	PEPTIDE TURN MIMETICS	

DECLARATION UNDER 37 C.F.R. §1.132

I, Ian D Jenkins, declare and say as follows:

1. I, Ian D Jenkins, received my Bachelor Degree with honours at the University of New South Wales, Sydney, Australia in 1966 and Doctorate from the University of New South Wales in 1969. I am currently a Professor of Chemistry at Griffith University which is located in Brisbane, Australia and am also the Deputy Director of Natural Product Discovery at the Eskitis Institute for Cell and Molecular Therapies located at the university. I have authored or co-authored 140 scientific publications, and am a named co-inventor on 2 patent applications.

2. I have conducted and supervised research in the area of chemical synthesis for the last 32 years with particular research interests being in the areas of the synthesis of biologically active molecules based on natural product scaffolds, medicinal chemistry, carbohydrate chemistry, organophosphorus chemistry (in particular the Mitsunobu reaction), polymer chemistry and reaction mechanisms.

3. I have been asked by Dr Peter Cassidy, to review a paper by Xin Ma et al (Prot. Peptide Lett., 1995, 347-350) and to provide my opinion on whether I consider that the cyclisation product from the Mitsunobu reaction as described in this paper is correct.

CONSIDERED: /Christopher Gross/ (06/21/2009)

4. I have been paid by Mimetica a consultancy fee for my time in reviewing the paper and preparing this declaration.

5. I understand that during prosecution of the above patent application in the US the Examiner has rejected claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138, and 140 on the basis of 35 U.S.C. §102(b) as being anticipated by Ma et al., 1995, Protein Peptide Letters, 2:347-350.

6. I attach in the appendix the structure of the Ma cyclisation precursor (compound 1 in the appendix), as well as structures of the Ma proposed cyclisation product (compound **2** in the appendix) as well as what I understand are the two cyclisation products thought to be the most likely by Dr Cassidy to be formed (structures **3** and **4** in the appendix).

7. I have examined the paper by Xin Ma et al (*Prot. Peptide Lett.*, **1995**, 347-350) and consider that the cyclisation product from the Mitsunobu reaction is certainly not the 1,4-diazepan-2-one structure (**2**) that they claim. Indeed I am surprised that this paper was accepted by the referee(s) as it is well known by those skilled in the art, that three and five-membered rings are far more easily formed than seven-membered rings (the rate of formation of five-membered rings is typically 10,000 times faster than for seven-membered rings – see Advanced Organic Chemistry by Carey and Sundberg, 3rd edition, Plenum, NY, 1990, p163). Given this fact, the referee(s) should have insisted that Ma et al provide evidence for the formation of a seven-membered ring. No such evidence was provided. The MS and microanalytical data provide evidence for the molecular formula, but not the structure. The ^{1}H NMR spectrum, was not assigned, and only provides evidence for a molecule with 43 protons.

8. Of the two possible structures that are proposed by Dr Cassidy, I am fairly certain that it is the N-Boc aziridine (**4**) that is formed, rather than the oxazoline (**3**) (see Scheme attached).

9. The ^{13}C chemical shift of the Boc carbonyl is very characteristic and where you would expect it to be (generally 161-163 ppm) for a Boc-aziridine [see S. Quader, S. E. Boyd, I. D. Jenkins, and T. A. Houston, *J. Org. Chem.*, 2007, **72**, 1962-1979; *J. Org. Chem.*, 2007, **72**, 1962; *J. Org. Chem.*, 2001, **66**, 1657; *J. Org. Chem.*, 1994, **59**, 4875; *J. Chem. Soc. Perkin 1*, 2001, 1916; *Tetrahedron* 2002, 5231; *Org. Lett.* 2001, **3**, 2349; *Synlett* 1998, 247]. I would expect the oxazoline to have a shift of about 157 ppm. Moreover, there are many examples of aziridine formation from hydroxy Boc-amines. A SciFinder substructure search gave no hits for oxazoline formation. The only literature examples of oxazoline formation are with amides (as in the paper by Galeotti et al, *Tet. Lett.*, 1992, 2807). There are no examples with N-Boc amines which are carbamates. Certainly, the ^{13}C chemical shift observed for the Boc carbonyl (160.7 ppm) is inconsistent with the structure (**2**) proposed by Ma et al. Such a structure would be expected to have a chemical shift for the Boc carbonyl very close to that of the starting material (**1**), ie, between 155 and 157 ppm.

10. I have also reviewed the hydrolysis experiments conducted on the cyclisation product by Dr Peter Cassidy as discussed in PCT application WO99/48913 on page 69. I understand that this PCT application corresponds to the US patent application the subject of this declaration.

11. In terms of the hydrolysis experiment (mild acid hydrolysis of the cyclised product with 0.1% aq. TFA at room temperature for 12 h to give back the starting material **1**), I consider that these conditions would not result in hydrolysis of the lactam **2** (Ma proposed structure) but would be consistent with an oxazoline **3**. However, this result is also consistent with an N-Boc aziridine **4**. In our experience, these have similar reactivities to epoxides (there is an example in our 2007 JOC paper where propylamine reacts selectively at room temperature with an N-Boc aziridine, but NaN_3 reacts with both the epoxide and the aziridine), and would be readily opened by mild acids.